pharmaceutical formulation comprising a therapeutically effective amount of a [pure] solid state Na^+, Li^+ or K^+ [alkaline] salt of the (-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5,-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole, and a pharmaceutically acceptable carrier.

In claims 47, 48 and 51, delete the expression "claims 42-44 or" and insert therefor -- claim 42 or 43 --.

In claim 49, delete "42-44 or 45" and insert therefor -- 42 or 43 --.

REMARKS

1. Claim Amendments

Applicants wish to thank the Examiner for the courtesy of the Interview that took place on April 13, 2000. The claims have been amended in the manner agreed upon by the participants of the Interview.

Specifically, claims 35, 36, 42 and 43 have been amended to define the active ingredient as the monovalent salt (Na^+, Li^+ or K^+) of the (-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5,-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole.

Claim 51 is objected to under 37 C.F.R. §1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. Claims 47-49 and 51 are multiple dependent claims and these claims have been amended to refer to other claims in the alternative and are not dependent upon another multiple dependent claim . It is deemed that the

form of amended multiple dependent claims 47-49 and 51 is proper. Accordingly, withdrawal of the objection under 37 C.F.R. §1.75(c) is requested.

Claims 42 and 45-49 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the subject matter which Applicants regard as the invention. Claim 42 has been amended to expressly recite a host for which the claimed method is administered. Claim 45 has been deleted. Therefore, the rejection has been obviated and withdrawal thereof is requested.

II. Claim Rejection – 35 U.S.C. §103

Claims 35-50 are rejected under 35 U.S.C. §103(a) as being unpatentable over DE 4,035,455 ("DE '455") in view of CA 117:90292. This obviousness rejection is of record and first appeared in the parent application, U.S. Patent Application. 08/899,931, filed July 24, 1997, now abandoned (the "'931 application"). The references were discussed by Applicants during the examination of the '931 application and in the Letter, mailed November 12, 1999, in the present application. Applicants rely on the comments of record.

The Examiner has maintained the obviousness rejection on the alleged basis that the Declaration of Tommy Andersson (hereinafter the "Declaration") is not convincing. On pages 2 and 3 of the Office Action, the Examiner provides four reasons why, in the Examiner's opinion, the Declaration is insufficient to overcome the obviousness rejection. However, these four reasons can be summarized as follows:

- the showing of Na salt in sterile solution by intravenous injection is not commensurate in scope with the claims which recite various alkaline salts for parenteral use (#1 of the Examiner's opinion, p. 2 of Office Action), and

- the comparative data showing that the (-)-enantiomer of omeprazole exhibited better activity than the racemate is expected (## 2-4 of the Examiner's opinion, p. 3 of the Office Action).

As noted in the Interview Summary (Paper No. 9), the obviousness rejection will be withdrawn in view of the amended claims and the Declaration. Claims 35, 36, 42 and 43 have been amended to define the active ingredient as the monovalent salt (Na^+, Li^+ or K^+) of the (-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5,-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole. Moreover, as set forth in the Declaration, the (-)-enantiomer of omeprazole when administered as a Na^+ salt has a different and more advantageous pharmacokinetic profile in terms of a higher AUC and lower interindividual variation when compared to the omeprazole racemate when administered as a Na^+ salt.

The observed difference in activity is unexpected in view of the prior art. In support of the non-obviousness of the claimed invention, Applicants rely on the article by Cairns et al. "Enantioselective high-performance liquid chromatographic determination of omeprazole in human plasma", Journal of Chromatography B, 666 (1995) 323-328. Cairns et al. measured the concentration of the (+)-enantiomer of omeprazole and the (-)-enantiomer of omeprazole after the intravenous administration of a 20 mg dose of omeprazole racemate. Cairns et al. reported that, when a racemic dose of omeprazole is administered intravenously, the concentration of (+)-omeprazole and (-)-omeprazole were essentially equal in the plasma samples that were assayed.

In response to the Examiner's request that Applicants identify the pertinent portions of the Cairns et al. article, the Examiner's attention is directed to the following statements in the publication at p. 327:

> Fig. 3 shows a representative graph of plasma concentrations of omeprazole enantiomers following administration of a 20-mg omeprazole i.v. dose. **It shows that when a racemic dose of omeprazole is administered, a similar ratio of enantiomers is observed in the clinical samples**...
>
> ...**The concentrations of (+)-omeprazole and (-)-omeprazole were essentially equal in the plasma samples assayed**...(Emphasis added)

The Cairns et al. article is not prior art. However, the later publication date (1995) supports Applicants position of non-obviousness. At the time the invention was made, the person of ordinary skill in the art would have expected the pharmacokinetic profile of the omeprazole racemate and of each enantiomer to be essentially same. The priority date of the claimed invention under 35 U.S.C. §119 is May 28, 1993.

(continued)

Furthermore, the Examiner's attention is directed to portions of the Declaration of Andersson, mailed February 12, 1997, in the grand-parent of the subject application, i.e., U.S. Patent No. 5,714,504 to Lindberg et al., issued February 3, 1998 (the "'504 patent").[1] The '504 patent is directed to pharmaceutical formulations for oral administration comprising an alkaline salt of the (-)-enantiomer of omeprazole. In the Declaration of Andersson in the '504 patent, the data demonstrated that the (-)-enantiomer of omeprazole had a different and more advantageous pharmacokinetic profile in terms of interindividual variation than both the (+)-enantiomer of omeprazole and the omeprazole racemate. According to the following excerpt from the Declaration of Andersson in the '504 patent, the advantageous pharmacokinetic profile of the(-)-enantiomer of omeprazole was unexpected:

> This [result] is contrary to the prior art teaching on the pharmacodynamic effect which was previously demonstrated in gastric glands to be the same for the two enantiomers as would be expected, (see Erlandsson, et al., Journal of Chromatography, 532 (1990) 305-319 p. 318), since the drug's mechanism of action involves a non-chiral active inhibitor formed in the compartments of the parietal cell with the same rate of reaction from both enantiomers. ***The non-chirality of the active form of omeprazole is an uncommon occurrence among chiral drugs where the activity usually resides in only one of the two enantiomers, the other being substantially less active***. (See, Declaration of Andersson at p. 3) (Emphasis added).

(continued)

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[1] A copy of the Declaration of Anderson was submitted on July 20, 1998 in the parent U.S. Patent Application Serial No. 08/899,931, now abandoned, of the subject application.

Therefore, the more advantageous pharmacokinetic profile of the (-)-enantiomer of omeprazole in terms of plasma concentrations and interindividual variation is unexpected in view of the prior art. This discovery was contrary to the state of the art which maintained that the concentration of the (+)- and the (-)-enantiomer of omeprazole, after the intravenous administration of omeprazole racemate, were essentially equal in the plasma samples that were assayed (See, Cairns et al.). Thus, the more advantageous pharmacokinetic profile of the (-)-enantiomer of omeprazole in terms of plasma concentrations and interindividual variation was indeed unexpected.

Neither the primary reference DE '455 or the secondary reference CA 117:90292, whether taken alone or in combination, suggests that the (-)-enantiomer of omeprazole when administered as a Na^+ salt would be more efficacious as the active ingredient of a pharmaceutical formulation for parenteral administration than either an alkaline salt of the omeprazole racemate or the (+)-enantiomer of omeprazole.

For all of the foregoing reasons, withdrawal of the rejection under 35 U.S.C. §103(a) is requested.

III. Obviousness-type Double Patenting Rejection

Claims 35-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent Nos. 5,900,424 to Källström et al. (the "'424 patent") and 5,877,192 to Lindberg et al. (the '192 patent"). The '424 patent is directed to the Mg^{2+} salt of omeprazole. In contrast, the claims have been amended to define the active ingredient as the monovalent salt (Na^+, Li^+ or K^+) of the (-)-enantiomer of omeprazole. Accordingly, Applicants respectfully submit that the claimed invention is not an obvious variant of

the '424 patent . Withdrawal of the obviousness-type double patenting rejection as to the '424 patent is requested.

In order to overcome the rejection as to the '192 patent, Applicants submit a Terminal Disclaimer whereby they disclaim the terminal part of any patent to be granted in the present application that would extend beyond the expiration date of the '192 patent. The Assistant Commissioner is authorized to charge Account Deposit No. 23-1703 in the amount of One Hundred and Ten Dollars ($110.00) pursuant to 37 C.F.R. §1.20(d) in connection with the filing of the Terminal Disclaimer.

As noted in the Office Action (paper No. 8), a Terminal Disclaimer was previously submitted and accepted as to the '504 patent.

Claims 35-50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting rejection as being unpatentable over claims of Applicants' co-pending application, U.S. Patent Application Serial No. 09/187,187,277. No action is presently required of Applicants since the cited '277 application is co-pending and has not yet in fact been patented.

CONCLUSION

Claims 35-37, 39-43 and 47-51 are directed to patentable subject matter. Accordingly, Applicants request reconsideration and allowance of the claims.

Any additional fee due in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: April 28, 2000

Respectfully submitted,

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